**HELICOBACTER PYLORI: EXPLORING ITS ANTIBIOTIC RESISTANCE AND ORDEAL IN GASTRIC ULCER AND CANCER.**

ABSTRACT

Helicobacter pylori; a gram-negative spiral-shaped bacterium, is involved in the pathogenesis of several gastrointestinal disorders, ranging from mild gastric ulcers to severe situations like chronic gastritis, MALT lymphoma, and gastric cancers. This review dives into the different factors contributing to the persistence of *H. pylori* and its growing antibiotic resistance. *Helicobacter pylori* causes cellular dysregulation and chronic inflammation, which are attributed to its virulence factors: CagA and VacA. These proteins, VacA and CagA, harm the host DNA repair systems, which raises the chances of malignant development by causing oxidative stress and epigenetic modifications. A major obstacle to the successful eradication therapy of *H. pylori* is its antibiotic resistance, which is linked to its capacity to create biofilms and activate efflux pumps. This renders typical treatment plans like the triple therapy, which involves omeprazole, amoxicillin, and clarithromycin, ineffective. The failure of current antibiotic therapy has increased the need for research into alternative treatments, techniques, and drugs, including potassium-competitive acid blockers and probiotic supplements, which have proven effective in improving eradication rates and lowering the recurrence of *H. pylori* infections. In addition, advanced diagnostic methods such as non-invasive molecular assays and next-generation sequencing now enable more precise determination of resistant profiles and help in the customization of therapeutic approaches against *H. pylori*. Insight into molecular and clinical data of *H. pylori* infections has highlighted the necessity for creative locally specific therapies that address the immediate pathogenic consequences as well as the more general issues of antibiotic resistance in *H. pylori*. This then emphasizes the significance of studies like this one that examine the resistance of *H. pylori* infections to antibiotics.

Keywords: *Helicobacter pylori, gastric ulcer, MALT lymphoma, antibiotics resistance, eradication therapy, biofilms.*

1. **INTRODUCTION**
   1. Background

Helicobacter pylori (*H. pylori*) is a gram-negative, spiral-shaped bacterium colonizing the stomach lining, affecting nearly half the global population. (Bauer, 2011) While many infections may remain asymptomatic, *H. pylori* is a known leading cause of chronic gastritis, peptic ulcer disease, and gastric cancer. The cognition of *H. pylori* as a key factor in this disease transformed gastroenterology, yet eliminating the bacterium is a major clinical challenge. (Wang, 2019)

The standard treatments involve a combination of antibiotics, such as clarithromycin or metronidazole, alongside a proton pump inhibitor and amoxicillin. However, resistance to these antibiotics has surfaced as a significant obstacle, which leads to persistent infections and increased disease burden. (Kouhsari, 2022) The resistance to clarithromycin and metronidazole has been reported worldwide, with rates exceeding 30% in some regions, reducing treatment efficacy and increasing recurrence rates. (De Francesco, 2019) This resistance is associated with point mutations in the 23S rRNA gene for clarithromycin and rdxA mutations for metronidazole, leading to treatment failures and persistent infections. (Wang, 2019) As the resistance spreads, treatment failures also become more frequent, leaving patients vulnerable to various complications, like ulceration and malignancy, which are noteworthy.

In response to this growth of antibiotic resistance crisis, researchers are exploring alternative strategies to improve *H. pylori* eradication. Probiotics, with the function of restoring gut microbiota balance and enhancing antibiotic effectiveness, have shown promise and results in reducing side effects and improving patient adherence. (Nabavi-Rad, 2022) Additionally, biofilm disruptors, such as N-acetylcysteine, may help weaken bacterial defenses, making them more susceptible to treatment. (Zaman, 2024) Understanding these strategies is essential for current and future efforts to combat antibiotic resistance and develop more effective therapies for *H. pylori*-associated diseases.

* 1. Aims and Objectives

This study aims to:

1. Examine the impact of *H. pylori* antibiotic resistance on treatment outcomes.
2. Investigate the link between antibiotic resistance and gastric ulcer progression.
3. Explore the potential of probiotics and biofilm disruptors as adjunct therapies.
4. Identify strategies to improve treatment efficacy and reduce antibiotic resistance.

With the resistance to antibiotics on the rise, the question remains: how can we effectively manage *H. pylori* infections in an era where the standard therapies are failing? This issue

is critical not only for preventing gastric ulcers and cancer but also for improving patient outcomes worldwide. By exploring resistance mechanisms and alternative treatments.

1. **MATERIALS AND METHODS**

This systematic review explored existing literature, clinical trials, and meta-analyses focusing on *Helicobacter pylori* antibiotic resistance and its relationship with gastric ulcers and cancer. The following methods were employed to identify, select, and analyze relevant studies.

#### 2.1. Search Strategy

We sourced articles from multiple databases, including PubMed, Sci-Hub, Google Scholar, Gavin Publishers, and MDPI (*Multidisciplinary Digital Publishing Institute*). The keywords used during the search process were:

* *H. pylori.*
* *Electrobacter pylori.*
* *Antibiotic resistance in gastric ulcer patients.*
* *Antibiotic resistance to H. pylori.*
* *H. pylori in connection to gastric ulcers and cancer.*

#### 2.2. Inclusion and Exclusion Criteria

Studies included in this review met the following criteria:

* Published between 2010 and 2025.
* Focused on human subjects with gastric ulcers or cancer, particularly those exhibiting antibiotic resistance related to *H. pylori*.
* Included clinical data on patients with gastric ulcers, patients who developed gastric ulcers, or patients who were resistant to treatment for gastric ulcers.

The exclusion criteria were as follows:

* Animal studies and animal clinical trials.
* Case reports and non-peer-reviewed articles.

#### 2.3. Selection Process

The selection of studies was conducted in three phases:

1. Title Screening: Initial screening involved reviewing the titles of retrieved articles to assess relevance to *H. pylori* antibiotic resistance, gastric ulcers, and cancer.
2. Abstract Screening: Articles with relevant titles underwent abstract screening further to evaluate their focus and alignment with the study topic.
3. Full-Text Screening: Full texts of selected articles were reviewed to confirm their eligibility based on the inclusion criteria. Articles that did not meet the specified criteria were excluded at this stage.

#### 2.4. Data Extraction

#### Data extraction followed a systematic approach. Information from the selected articles was gathered by reviewing the title, abstract, and full text to ensure alignment with the review topic: "*Exploring Helicobacter pylori Antibiotic Resistance and Its Role in Gastric Ulcer and Cancer.*" Relevant data related to *H. pylori* antibiotic resistance patterns, clinical outcomes in gastric ulcer patients, and associations with cancer development were collected for analysis.

1. **RESULTS AND DISCUSSION**
   1. RESULTS
2. Impact of Antibiotic Resistance on Treatment:

Antibiotic resistance, especially to clarithromycin and metronidazole, significantly reduces treatment success for *H. pylori*. With resistance rates exceeding 30%, many patients face persistent infections and repeated treatment attempts.

1. Link to Gastric Ulcers and Complications:

Resistant *H. pylori* infections lead to chronic inflammation, increasing the risk of peptic ulcers and potentially gastric cancer. Mutations in the 23S rRNA and rdxA genes are key to treatment failures.

1. Promise of Probiotics and Biofilm Disruptors:
   1. Probiotics (like Lactobacillus) help reduce side effects, restore gut health, and improve treatment adherence.
   2. N-acetylcysteine (NAC) weakens bacterial defenses, making them easier to eliminate when combined with antibiotics

Antibiotic resistance in *H. pylori* demands new strategies. Combining probiotics, biofilm disruptors, and personalized treatment offers hope for better outcomes and lower risks of gastric ulcers and cancer.

* 1. STRATEGIES FOR BETTER OUTCOMES

1. Tailoring treatments based on antibiotic susceptibility testing (AST).
2. Using quadruple therapy for resistant cases.
3. Adding probiotics and biofilm disruptors to improve results.
4. Educating patients to stick to prescribed therapies.
   1. DISCUSSION
      * 1. **Tailoring Treatments Based on Antibiotic Susceptibility Testing in Gastric Ulcer Management.**

The emergence of antibiotic resistance in *H. pylori* infections underscores the need for AST to ensure effective treatment (Malfertheiner et al., 2021). When patients are given a generic, one-size-fits-all antibiotic regimen, there is a significant risk of failure due to underlying resistance (Megraud et al., 2021). AST enables clinicians to choose the right antibiotics from the start, improving success rates and minimizing unnecessary exposure to ineffective medications (Liou et al., 2019). Rapid molecular testing methods, such as next-generation sequencing, provide faster and more accurate susceptibility results, allowing for timely treatment decisions (Savoldi et al., 2018). However, there are still barriers to widespread adoption, including accessibility and cost (Graham & Fischbach, 2010). Many healthcare facilities lack the infrastructure for routine AST, leading to continued reliance on empirical therapies (Megraud et al., 2021). From a patient's perspective, failed treatments are frustrating, costly, and can prolong discomfort (Liou et al., 2019). Repeated courses of antibiotics not only increase resistance but also lead to unwanted side effects like diarrhea and gut microbiome disruption (Malfertheiner et al., 2021). By shifting toward AST-driven care, we can significantly improve patient outcomes and combat the growing problem of antibiotic resistance (Savoldi et al., 2018).

* + - 1. **Using Quadruple Therapy for Resistant Cases.**

Quadruple therapy, which typically includes a proton pump inhibitor (PPI), bismuth, and two antibiotics, has emerged as a first-line treatment in regions with high rates of clarithromycin resistance. The Maastricht IV consensus guidelines recommend this approach due to its improved efficacy compared to standard triple therapy, especially in areas where antibiotic resistance is prevalent (Lü et al., 2016). Combining these agents targets the bacterium more effectively and mitigates the risk of treatment failure associated with antibiotic resistance (Lau et al., 2016). Furthermore, studies have shown that quadruple therapy can lead to higher eradication rates and lower recurrence of infection, making it a viable option for managing resistant *H. pylori* cases (Hamzavi & Bashiri, 2023).

* + - 1. **Adding Probiotics and Biofilm Disruptors to Improve Results.**

Incorporating probiotics into the treatment regimen has been shown to enhance the effectiveness of quadruple therapy. Probiotics, such as *Lactobacillus* and *Bifidobacterium* strains, have demonstrated the ability to improve gut microbiota balance, reduce antibiotic-associated side effects, and increase *H. pylori* eradication rates (Lau et al., 2016; Jung et al., 2018). For instance, a meta-analysis indicated that adding probiotics can significantly improve eradication rates when used alongside standard therapies (Lau et al., 2016). Probiotics may also help maintain gastrointestinal health during antibiotic treatment, thereby improving patient compliance and overall treatment outcomes (Hassan et al., 2022). In addition, the role of biofilm in *H. pylori* infections cannot be overlooked, as biofilm formation significantly contributes to antibiotic resistance. *H. pylori* can form biofilms on the gastric mucosa, which protect the bacteria from the effects of antibiotics, leading to treatment failure (Ji & Yang, 2021). Recent studies have explored the use of biofilm disruptors, such as *phillygenin*, which has been shown to inhibit biofilm formation and enhance the susceptibility of *H. pylori* to antibiotics (Li et al., 2022). By integrating biofilm disruptors into treatment regimens, clinicians may be able to overcome the challenges posed by biofilm-associated resistance, thereby improving the efficacy of quadruple therapy. (Hou et al., 2022). Moreover, the combination of probiotics and biofilm disruptors presents a promising avenue for enhancing *H. pylori* eradication strategies. Probiotics can potentially disrupt biofilm formation by competing for adhesion sites on the gastric epithelium and producing substances that inhibit *H. pylori* growth (Cervantes‐Elizarrarás et al., 2019). This synergistic effect could lead to improved treatment outcomes, particularly in patients with antibiotic-resistant strains of *H. pylori* (Jung et al., 2018). Clinical trials have indicated that the use of probiotics alongside standard therapies not only increases eradication rates but also reduces the incidence of adverse effects associated with antibiotic treatment (Hamzavi & Bashiri, 2023; Lau et al., 2016).

* + - 1. **Educating Patients to Stick to Prescribed Therapies.**

Successful eradication of Helicobacter pylori (*H. pylori*) depends largely on patient adherence to prescribed therapies. Studies show that patients who complete their full course of treatment have significantly higher eradication rates compared to those who do not. Educating patients on the importance of adherence is crucial in preventing treatment failure, recurrence, and antibiotic resistance (Shah et al., 2021). Non-adherence often results from factors such **as side effects, complex dosing schedules, and a lack of understanding of the risks of incomplete treatment**. Patients who stop therapy prematurely are at a higher risk of persistent infection, leading to complications like peptic ulcers and, in severe cases, gastric cancer. Additionally, improper antibiotic use contributes to the emergence of drug-resistant H. pylori strains, making future treatment more challenging.

To improve adherence, healthcare providers should emphasize **clear patient education**—explaining the consequences of incomplete therapy and addressing concerns about side effects (Haguet et al., 2024). **Simplified dosing regimens, reminders, and follow-up consultations** can also help patients complete their treatment successfully. By ensuring that patients are well-informed and supported, the effectiveness of *H. pylori* eradication therapies can be maximized (Zeng et al., 20230).

**CONCLUSION**

*Helicobacter pylori's* increasing antibiotic resistance presents a formidable challenge to standard eradication regimens, particularly those involving clarithromycin and metronidazole. Resistance mechanisms, including genetic mutations and biofilm formation, contribute to persistent infections, reduced treatment efficacy, and a heightened risk of complications such as gastric ulcers and cancer. These factors necessitate a paradigm shift in *H. pylori* management, emphasizing precision medicine and innovative therapeutic strategies. This review underscores the importance of antibiotic susceptibility testing (AST) as a fundamental tool in optimizing treatment selection and improving patient outcomes. The implementation of AST-driven therapy allows for the selection of the most effective antibiotics, reducing treatment failure and minimizing unnecessary antibiotic exposure. Furthermore, adjunctive therapies such as probiotics and biofilm disruptors have demonstrated potential in enhancing eradication rates and mitigating the adverse effects associated with prolonged antibiotic use. The adoption of bismuth-based quadruple therapy in regions with high resistance rates also offers a promising alternative, particularly in cases where conventional triple therapy proves ineffective. A comprehensive approach that integrates AST, alternative treatment modalities, and patient adherence strategies is essential to overcoming the challenges posed by antibiotic resistance. Future research should focus on refining diagnostic tools, exploring novel therapeutic agents, and improving public health initiatives to curb the emergence of resistant *H. pylori* strains. By leveraging these strategies, the medical community can enhance treatment efficacy, reduce recurrence rates, and mitigate the long-term consequences of *H. pylori-*associated diseases.

**References**

Ali, A., & AlHussaini, K. I. (2024). *Helicobacter pylori*: A Contemporary Perspective on Pathogenesis, Diagnosis and Treatment Strategies. *Microorganisms*, *12*(1), 222. <https://doi.org/10.3390/microorganisms12010222>

Amin, D. H. M. (2021). Current techniques and future directions in antibiotic resistance breakers. International Journal of Medical, Pharmacy and Drug Research, 5(4), 16-21. <https://dx.doi.org/10.22161/ijmpd.5.4.3>

Bauer, B., & Meyer, T. F. (2011). The human gastric pathogen Helicobacter pylori and its association with gastric cancer and ulcer disease. Ulcers, 2011(1), 340157.23 pages, 2011. <https://doi.org/10.1155/2011/340157>

Cervantes‐Elizarrarás, A., Cruz‐Cansino, N., Ramírez‐Moreno, E., Vega-Sánchez, V., Velázquez‐Guadarrama, N., Zafra‐Rojas, Q., … & Piloni‐Martini, J. (2019). In vitro probiotic potential of lactic acid bacteria isolated from aguamiel and pulque and antibacterial activity against pathogens. Applied Sciences, 9(3), 601. https://doi.org/10.3390/app9030601

Dascălu, R. I., Bolocan, A., Păduaru, D. N., Constantinescu, A., Mitache, M. M., Stoica, A. D., & Andronic, O. (2023). Multidrug resistance in Helicobacter pylori infection. *Frontiers in Microbiology*, *14*. <https://doi.org/10.3389/fmicb.2023.1128497>

De Francesco, V., Zullo, A., Fiorini, G., Saracino, I. M., Pavoni, M., & Vaira, D. (2019). Role of MIC levels of resistance to clarithromycin and metronidazole in Helicobacter pylori eradication. Journal of Antimicrobial Chemotherapy, 74(3), 772-774., <https://doi.org/10.1093/jac/dky469>

Elbehiry, A., Abalkhail, A., Anajirih, N., Alkhamisi, F., Aldamegh, M., Alramzi, A., AlShaqi, R., Alotaibi, N., Aljuaid, A., Alzahrani, H., Alzaben, F., Rawway, M., Ibrahem, M., Abdelsalam, M. H., Rizk, N. I., Mostafa, M. E. A., Alfaqir, M. R., Edrees, H. M., & Alqahtani, M. (2024). *Helicobacter pylori*: Routes of Infection, Antimicrobial Resistance, and Alternative Therapies as a Means to Develop Infection Control. *Diseases*, *12*(12), 311. <https://doi.org/10.3390/diseases12120311>

Graham, D. Y., & Fischbach, L. (2010). "Helicobacter pylori treatment in the era of increasing antibiotic resistance." Gut, 59(8), 1143-1153.

Hamzavi, Y. and Bashiri, H. (2023). The effect of quadruple therapy plus probiotics on helicobacter pylori eradication and antibiotic-associated side effects: a randomized placebo-controlled trial. Journal of Kermanshah University of Medical Sciences, 27(4). <https://doi.org/10.5812/jkums-137908>

Hassan, S., Uddin, M., Kaunaine, M., Sultana, S., Samreen, S., & Mohiuddin, M. (2022). A comparative prospective study in the management of helicobacter pylori infection using lactobacillus reuteri vs conventional therapy. Journal of Drug Delivery and Therapeutics, 12(3-S), 123-128. <https://doi.org/10.22270/jddt.v12i3-s.5158>

Hou, C., Yin, F., Wang, S., Zhao, A., Li, Y., & Liu, Y. (2022). Helicobacter pylori biofilm-related drug resistance and new developments in its anti-biofilm agents. Infection and Drug Resistance, Volume 15, 1561-1571. <https://doi.org/10.2147/idr.s357473>

Huguet, J. M., Ferrer‐Barceló, L., Suárez, P., Barcelo‐Cerda, S., Sempere, J., Saracino, I. M., Fiorini, G., Vaira, D., Pérez‐Aísa, Á., Jonaitis, L., Tepes, B., Castro‐Fernandez, M., Pabón‐Carrasco, M., Keco‐Huerga, A., Voynovan, I., Lucendo, A. J., Lanas, Á., Martínez‐Domínguez, S. J., Almajano, E. A., . . . Gisbert, J. P. (2024). Role of compliance in Helicobacter pylori eradication treatment: Results of the European Registry on H. pylori management. *United European Gastroenterology Journal*, *12*(6), 691–704. <https://doi.org/10.1002/ueg2.12569>

Ji, J., & Yang, H. (2021). In Vitro Effects of Lactobacillus plantarum LN66 and Antibiotics Used Alone or in Combination on Helicobacter pylori Mature Biofilm. *Microorganisms*, *9*(2), 424. <https://doi.org/10.3390/microorganisms9020424>

Jung, J. H., Cho, I. K., Lee, C. H., Song, G. G., & Lim, J. H. (2017). Clinical Outcomes of Standard Triple Therapy Plus Probiotics or Concomitant Therapy for Helicobacter pylori Infection. *Gut And Liver*, *12*(2), 165–172. <https://doi.org/10.5009/gnl17177>

Kim, J. Y., Kim, N., Park, H. K., Jo, H. J., Shin, C. M., Lee, S. H., Park, Y. S., Hwang, J. H., Kim, J. W., Jeong, S. H., Lee, D. H., Nam, R. H., Kim, J. M., Lee, J. H., Jung, H. C., & Song, I. S. (2011). The Korean journal of gastroenterology = Taehan Sohwagi Hakhoe chi, 58(2), 74–81. <https://doi.org/10.4166/kjg.2011.58.2.74>

Kouhsari, E., Sadeghifard, N., Khadiv, A., Sayadi, H., Amiriani, T., Ghafourian, S., & Krutova, M. (2022). Heteroresistance to clarithromycin and metronidazole in patients with a Helicobacter pylori infection: a systematic review and meta-analysis. Annals of Clinical Microbiology and Antimicrobials, 21(1), 19. <https://doi.org/10.1186/s12941-022-00509-3>

Lau, C., Ward, A., & Chamberlain, R. (2016). Probiotics improve the efficacy of standard triple therapy in the eradication of Helicobacter pylori: a meta-analysis. *Infection and Drug Resistance*, *Volume 9*, 275–289. <https://doi.org/10.2147/idr.s117886>

Li, R., Qin, C., Huang, G., Liao, L., Mo, X., & Huang, Y. (2022). Phillygenin inhibits helicobacter pylori by preventing biofilm formation and inducing ATP leakage. Frontiers in Microbiology, 13. <https://doi.org/10.3389/fmicb.2022.863624>

Liou, J. M., et al. (2019). "Tailored versus empirical therapy for Helicobacter pylori eradication: A multicenter, open-label, randomized trial." The Lancet Gastroenterology & Hepatology, 4(9), 707-715.

Lü, M., Yu, S., Deng, J., Yan, Q., Yang, C., Guo-dong, X., … & Zhou, X. (2016). Efficacy of probiotic supplementation therapy for helicobacter pylori eradication: a meta-analysis of randomized controlled trials. PLOS One, 11(10), e0163743. <https://doi.org/10.1371/journal.pone.0163743>

Malfertheiner, P., et al. (2021). "Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report." Gut, 70(1), 17-34.

Megraud, F., et al. (2021). "Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption." Gut, 70(10), 1815-1822.

Nabavi-Rad, A., Sadeghi, A., Asadzadeh Aghdaei, H., Yadegar, A., Smith, S. M., & Zali, M. R. (2022). The double-edged sword of probiotic supplementation on gut microbiota structure in Helicobacter pylori management. Gut Microbes, 14(1). <https://doi.org/10.1080/19490976.2022.2108655>

Ng, H.-Y., Leung, W. K., & Cheung, K.-S. (2023). Antibiotic Resistance, Susceptibility Testing and Stewardship in *Helicobacter pylori* Infection. *International Journal of Molecular Sciences*, *24*(14), 11708. <https://doi.org/10.3390/ijms241411708>

Rao J, Zhan C, Yang J, Huang Y, Chen D, et al. (2023) Overcoming Antibiotic Resistance in Helicobacter Pylori: The Promise of Non-Antibiotic Therapies. J Dig Dis Hepatol 8: 194. <https://doi.org/10.29011/2574-3511.100094>

Savoldi, A., et al. (2018). "Prevalence of antibiotic resistance in Helicobacter pylori: A systematic review and meta-analysis in World Health Organization regions." Gastroenterology, 155(5), 1372-1382.

Seo, J. H., Woo, H. O., Youn, H. S., & Rhee, K. H. (2014). Antibiotics resistance of Helicobacter pylori and treatment modalities in children with *H. pylori* infection. Korean journal of pediatrics, 57(2), 67–71. <https://doi.org/10.3345/kjp.2014.57.2.67>

Shah, S. C., Iyer, P. G., & Moss, S. F. (2021). AGA Clinical Practice Update on the Management of Refractory Helicobacter pylori Infection: Expert Review. *Gastroenterology*, *160*(5), 1831–1841. <https://doi.org/10.1053/j.gastro.2020.11.059>

Sharndama, H.C., Mba, I.E. *Helicobacter pylori*: an up-to-date overview on the virulence and pathogenesis mechanisms. *Braz J Microbiol* 53, 33–50 (2022). <https://doi.org/10.1007/s42770-021-00675-0>

Wang, D., Guo, Q., Yuan, Y., & Gong, Y. (2019). The antibiotic resistance of Helicobacter pylori to five antibiotics and influencing factors in an area of China with a high risk of gastric cancer. BMC microbiology, 19, 1-10. <https://doi.org/10.1186/s12866-019-1517-4>

Zaman, T., Haq, A., Ahmad, R., Sinha, S., Chowdhury, K., Parvin, S., Imran, M., Humayra, Z. U., Kumar, S., & Haque, M. (2024). The Role of Probiotics in the Eradication of Helicobacter pylori and Overall Impact on Management of Peptic Ulcer: A Study Involving Patients Undergoing Triple Therapy in Bangladesh. Cureus, 16(3), e56283. <https://doi.org/10.7759/cureus.56283>

Zeng, R., Li, X., Wang, F., Xie, J., Song, C., & Xie, Y. (2023). Reinforced medication adherence improves Helicobacter pylori eradication rate in developing countries: A systematic review and meta-analysis of randomized controlled trials. *Helicobacter*, *28*(4), e12989. <https://doi.org/10.1111/hel.12989>